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Review article: the design of clinical trials in hepatic encephalopathy - an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement

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Summary

Background—The clinical classification of hepatic encephalopathy is largely subjective, which has led to difficulties in designing trials in this field.

Aims—To review the current classification of hepatic encephalopathy and to develop consensus guidelines on the design and conduct of future clinical trials.

Methods—A round table was convened at the 14th International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) meeting. Key discussion points were the nomenclature of hepatic encephalopathy and the selection of patients, standards of care and end-points for assessing the treatment and secondary prevention of hepatic encephalopathy.

Results—It was generally agreed that severity assessment of hepatic encephalopathy in patients with cirrhosis, whether made clinically or more objectively, should be continuous rather than categorical, and a system for assessing the SONIC (Spectrum of Neuro-cognitive Impairment in Cirrhosis) was proposed. Within this system, patients currently classified as having minimal hepatic encephalopathy and Grade I hepatic encephalopathy would be classified as having Covert hepatic encephalopathy, whereas those with apparent clinical abnormalities would continue to be classified as overt hepatic encephalopathy. Some aspects of the terminology require further debate. Consensus was also reached on the patient populations, standards of care and endpoints to assess clinical trial outcomes. However, some compromises had to be made as there is

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considerable inter- and intravariability in the availability of some of the more objective surrogate performance markers.

Conclusions—The objectives of the round table were met. Robust, defendable guidelines for the conduct of future studies into hepatic encephalopathy have been provided. Outstanding issues are few and will continue to be discussed.

Introduction

There are several issues related to the performance of clinical trials in hepatic encephalopathy (HE) that have impeded progress in the field. The main objective of this round table was to provide, as far as possible, under the auspices of International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN), consensus guidelines on classification of HE and on the design and conduct of future possible clinical trials. The round table discussion took place during the 14th ISHEN conference held between 14 and 18 September 2010 at Val David, Quebec, Canada.

There were three main discussants, Drs Juan Cordoba, Kevin Mullen and Marsha Morgan, whose related presentations set the stage for a vigorous discussion among the attendees in the presence of several ISHEN members (Appendix), including the President Dr Roger Butterworth and the President-elect Dr Hendrik Vilstrup. Drs Debbie Shawcross, Piero Amodio and Jasmohan Bajaj also provided additional input. Dr Jasmohan Bajaj transcribed the proceedings and produced the first draft of this document for circulation to authors. On some points, there was a clear consensus but on others there was still debate and these important areas are highlighted.

Current Classification of He And Proposed Modifications of the Terminology

The classification proposed by the 18th World Congress was largely upheld and agreed on by members present.[1, 2] Discussions held pertained strictly to Type C or cirrhosis-associated HE.

Currently, these patients are classified as having either overt or minimal HE. Overt or clinically apparent HE manifests as a neuropsychiatric syndrome encompassing a wide spectrum of mental and motor disorders. It may arise episodically over a period of hours or days in patients who have previously been stable. Patients may return to normal following an episode of overt HE; however, many will retain some degree of clinical, neuropsychometric or neurophysiological impairment in the longer term, particularly those with severely decompensated liver disease.[3] Less frequently, patients present with persistent neuropsychiatric abnormalities, which remain stable over time. Individuals with overt HE also show a wide spectrum of other abnormalities, including impaired psychomotor performance, disturbed neurophysiological function and altered neural imaging, the results of which do not necessarily correlate with one another or with the degree of impairment observed clinically, although, in general, the degree of impairment in the individual test modalities increases as the clinical condition worsens.

The term minimal HE is used to describe patients with cirrhosis who are ‘clinically normal’ but who show abnormalities of cognition and/or neurophysiological variables. The presence of minimal HE is not without consequence. It has a detrimental effect on health-related quality of life (HRQoL)[4] and the ability to perform complex tasks, such as driving,[5] and predisposed to the development of overt HE.[6] Alternatives such as the terms ‘latent’ or ‘subclinical’ were mooted but there was no clear consensus and so the term minimal HE is to be retained for the present.

The key differentiator between overt and minimal HE is the presence of change in mental state. These are usually assessed using the West-Haven grading system[7, 8] (Table 1). All speakers reiterated the intense subjectivity of this system, which classifies mental status into categories that may or may not be reproducibly applied in clinical practice or in multicentre trials. Specifically, the extreme inter- and intra-observer variability between identifying patients with Grade I of the West-Haven criteria[7, 8] was considered to be a major stumbling block.[2, 9, 10]

The distinction between Grades I and II HE is made more readily particularly if the operative definitions proposed by Amodio *et al*.,[11] which highlight the importance of the presence of disorientation, are used. It was noted that Hassanein *et al*.[9] reported good inter-centre reliability in the assessment of disorientation to time in Grade II HE in their recent multicentre trial. Thus, as the differentiation between minimal and Grade I HE is not reliable, but there is good inter-rater reproducibility in the identification of Grade II HE it was suggested that patients with minimal HE and Grade I HE should be grouped together. There was considerable debate over the terminology to be used to describe this conjoined group. Suggestions included low-grade and covert. The term covert was not favoured by some as it implied that the patient might have been aware of changes but were keeping them hidden; in addition the word does not translate into Italian or Spanish with ease. The term low-grade was felt to perhaps trivialise the condition in much the same way as the use of the term minimal. However, despite the lack of consensus, ‘covert’ was chosen as the term to be applied to this conjoined group and will be used as such in the rest of the document (Table 2).

Further debate ensued aimed at refining the criteria for definition of this ‘covert’ group. Asterixis (flapping tremor) is perhaps the best known physical sign of HE. As the intension was to use the term covert HE to define patients who exhibited no obvious clinical features of HE, then clearly patients who exhibited this feature would not be included. Thus, the term covert HE would be used as an umbrella under which to describe patient with cirrhosis with neuropsychometric/neurophysiological abnormalities in the absence of disorientation and asterixis (Figure 1).

Finally, it was generally agreed that the presence of Grade II HE requires therapeutic intervention but that patients with covert HE are generally not treated. Thus, trials in patients with covert HE could be placebo-controlled.

Categorical vs. Continuous classification of the severity of HE

It was generally agreed that the current categorical approach used to classify the severity of HE is limited by difficulties in establishing thresholds and boundaries. Consideration was therefore given to the possibility of considering the neuro-cognitive changes in cirrhosis as a spectrum of change rather than one defined by categories. The system proposed for assessing the Spectrum of Neuro-cognitive Impairment in Cirrhosis has the acronym SONIC (Figures 1 and 2).[12, 13]

Using the SONIC classification, patients who are impaired would be further classified as stable or unstable. Unstable patients are defined as those who were previously stable but who over hours and possibly days develop clinically discernable features of HE and require medical attention and possible hospitalisation, so-called episodic HE. Stable patients are defined as those who have covert or overt evidence of HE but in whom there is little day-to-day fluctuation in their status. The majority of the patients exhibiting stable overt HE are independent in their daily activities. A small number may, however, exhibit severe limitation of their functional capacity either because of persistent but stable impairment of their

cognitive state or because of significant motor problems. Many of these patients have extensive portal-systemic shunting.[14] In some, the shunt may have been surgically created or inserted as a TIPS (Transjugular Intrahepatic Portosystemic Shunt). Parkinsonian features may be prominent with a fine tremor unaffected by intention, pronounced rigidity, staccato speech and a shuffling gait.[15–17] Cerebellar features are also common and manifest as gait disturbance, truncal ataxia, an intention tremor and dysarthria. Involuntary choreoathetoid movements may be observed. Some may develop a progressive spastic paraparesis without sensory impairment or sphincter dysfunction, so-called hepatic myelopathy, which may or may not be accompanied by cognitive impairment.

There was considerable debate about the terminology that should be applied to this small group of patients with stable, persistent but disabling cognitive and/or motor change. Some favoured use of the term dementia to describe those with persisting cognitive impairment, which rendered them incapable of independent living. However, dementia is, by definition, irreversible and these patients have been shown to regain cognitive function following hepatic transplantation.[18] The term acquired non-Wilsonian hepato-cerebral degeneration was suggested for those patients with prominent motor problems with cognitive impairment. However, liver transplantation is also associated with reversal of even major incapacitating Parkinsonian features resistant to treatment[19, 20] and indeed of the spastic paraparesis associated with the presence of hepatic myelopathy.[21, 22] All parties conceded that although this small population of patients were easily identified, the nosology was difficult. These patients have stable, persistent, often incapacitating cognitive/motor abnormalities and are difficult to manage using conventional treatment. The terminology to be applied to this group will continue to be debated.

Despite the relatively minor difficulties highlighted, there was unanimous agreement that the severity of HE, whether assessed using clinical scales, psychometry, or neurophysiological variables, should be classified as a continuum. All of the assessment tools provide an index of severity that does not need to be limited by categories that, in the event, can not be adequately defined.

Therapeutic Trials in HE

Three types of therapeutic trials were considered (i) management of hospitalised patients with episodic HE; (ii) secondary prophylaxis in patients following an episode of HE; and (iii) management of minimal/covert HE. In each case, consideration was given to the conduct of both large-scale multicentre trials with clinical outcomes and smaller scale ‘proof of concept’ trials, which tend to have more pathophysiological endpoints. Where possible, criteria were identified for (i) the selection of the trial populations; (ii) the optimal standard of care that should be applied; and (ii) the trial endpoints

Management of episodic HE

It was generally acknowledged that these trials are extremely difficult to undertake primarily because management of the factor(s) that precipitated the event may be sufficient to resolve the HE.

Potential patient populations—Three potential groups of in-patients with HE were considered:

- **i.** those not expected to survive hospitalisation;
- **ii.** those with acute-on-chronic liver failure (ACLF); and

iii. those with a clear-cut episode of HE, either spontaneous occurring or precipitated by an event such as variceal haemorrhage.

It was unanimously agreed that patients with HE, not expected to survive their hospital admission, should be excluded from treatment trials.

There were more detailed discussions about the possible inclusion of patients with ACLF.[23] Although it was recognised that the exact definition of ACLF has yet to be agreed on, the presence of dysfunction in another organ, in addition to the liver, for example the kidney, would be indicative of ACLF.[24] One of the most important issues debated on was whether it would be acceptable to consider reversal of HE as an suitable endpoint in treatment trials, which include these patients. Survival is undoubtedly the most important and valid endpoint for patients with ACLF as the only definitive treatment for his condition is hepatic transplantation.[23] In addition, there is also the possible confounding fact that HE might improve incidentally as a result of treatment of other features of the ACLF such as infection or electrolyte disturbances, and this would confound the results; this being said, it was also agreed that improving HE in this patient population may favour bridge time to transplantation, may improve HRQoL and might shorten both the time spent in the intensive care unit (ICU) and the overall length of hospital stay. Thus, although it was agreed that patient with ACLD should not be included in treatment trials in HE, it was agreed that they should not be excluded from small-scale proof-of-concept trials or trials directed at exploring pathophysiological mechanisms of HE.

Thus, the ideal candidates for these studies are patients who were previously clinically stable but who over a period of hours or days develop clinically apparent HE either spontaneously or as a result of an obvious precipitant, such as infection or variceal bleeding, and require hospitalisation.

Optimal standard of care—It was generally agreed that all patients should be managed using a set protocol that should include:[25, 26]

i. the identification of other potential causes for their altered mental state, head injury or drug intoxication;

ii. the identification and management of any potential precipitating factors, for example, constipation, metabolic abnormalities, infection or bleeding; and

iii. sontinuous monitoring of the underlying liver function and access to liver transplantation.

Therefore, any new specific therapy for HE, which is the focus of a trial should not ideally be started for at least 24–48 h after the institution of optimal standard of care therapy and only in those patients in whom mental status' abnormalities persist or are not improving as expected[27] Specific concerns were raised, however, that if appropriately carried out, these standard of care procedures would improve mental status in the majority of patients rendering them ineligible for HE-specific treatment trials.[25, 27] In consequence, it was agreed that provided that the optimal standard of care was instituted, treatment trial could be initiated earlier if they include a placebo comparator. This would allow evaluation of the new treatment as an adjuvant to standard treatment. This approach is supported by both anecdotal evidence and recently published experience, which have prompted a call for placebo-controlled trials in HE.[28, 29]

Endpoints to define outcome—A number of possible endpoints were discussed, bearing in mind that these would invariably be dictated by the nature of the trials to be undertaken. Thus, endpoints would need to be tailored specifically to address the trial

objectives; clearly different endpoint might be appropriate in large-scale clinical investigations and small-scale proof-of-concept trials.

In all such studies, however, in-hospital and remote survival is one of the most important primary endpoints; mortality should be recorded for both liver-related and total deaths. In addition, changes in mental state and the rate of recovery should be recorded as primary endpoints. Mental state should be assessed using simple scales, which could be the modified West Haven criteria described earlier[11] and the Glasgow Coma score.[30] The evaluation of mental status should be carried out at least two to four times daily to allow determination of the rate of improvement. The HESA (Hepatic Encephalopathy Scoring Algorithm) is a clinical grading scale, which was used in a recent randomised trial, but its use has not been fully validated.[10, 31] Other easily obtained endpoints for comparison could include the number of days in the ICU, the length of hospital stay (LOS), HRQoL and cost analyses. A variety of surrogate markers, which are discussed more fully in the section on minimal/covert HE, such as the electroencephalogram (EEG) and psychometric tests could also be employed to monitor changes more objectively, provided that the techniques have been standardised and validated for use in the participating centres.[32] Individual centres may wish to utilise additional, validated test systems to which they have access and with which they are familiar. Differences in outcome in relation to the nature of the precipitant could be contemplated in patients in whom a clear precipitant can be identified. However, such studies would have to be very large to allow for meaningful comparisons.

Proof-of-concept trials will undoubtedly need to be monitored more specifically using tools that relate best to the endpoints anticipated or expected. This might require neural imaging and assessment of circulating blood markers in addition to more routinely utilised modalities.[32]

Recommendations for trials in patients with episodic HE

- **i.** Patients who are terminally ill or have ACLF should be excluded.
- **ii.** A detailed standard of care algorithm must be agreed a priori and must be instituted and monitored diligently throughout the trial.
- **iii.** Ideally, patients should not be entered into trials until at least 24–48 h after the institution of optimal standard-of-care therapy and then only if their mental state abnormalities persist or are not improving as expected.
- **iv.** Provided the optimal standard of care is instituted and maintained, treatment trial can be initiated earlier if they include a placebo comparator; this would allow an evaluation of the trial treatment as an adjuvant to standard therapy.
- **v.** Large-scale, multicentre treatment trials should be evaluated using robust clinical outcomes such as in-hospital and remote survival, liver-related and total deaths, completeness and speed of recovery from HE, number of days in ICU, total LOS, HRQoL and associated costs. More objective surrogate markers for HE, such as psychometric testing, can be employed if standardised and validated tools are available for use in all centres. Individual centres can utilise additional, accessible, validated markers if they choose.
- **vi.** Proof-of-concept trials will additionally be monitored using tools that best relate to the endpoints anticipated or expected; this may involve use of neural imaging or measurement of specific bio-markers.

Secondary prophylaxis for HE

It was unanimously agreed that trials for secondary prophylaxis for HE should be randomised and placebo-controlled. Otherwise, the specific discussion points were similar to those raised for episodic HE; consensus was achieved on the following, which as there was no contention, will serve as recommendations:

Patient population—Ideally, out-patients stabilised after one or more episodes of HE requiring medical attention or hospitalisation and show little or no evidence of discernable HE. These patients may or may not be receiving maintenance treatment with, for example, a non-absorbable disaccharide and/or rifaxamin.

Standard of care—Standards of care differ across countries and institutions. Although there is evidence for the prophylactic efficacy of non-absorbable disaccharides, with or without rifaxamin, patients who have experienced at least one previous episode of overt HE are not necessarily prescribed medication nor are they necessarily compliant with its use[10, 33] Thus, in any trial Trials in patients with minimalin this field, it is important to establish whether patients are on a stable treatment regimen or not. If patients are receiving prophylactic treatment already, then any new agent will be evaluated as adjuvant therapy. If these patients are not receiving prophylactic treatment, then the new medication will be evaluated as a stand-alone treatment. Thus, either the standard of care must be uniformly applied or else the patient population will need to be large enough to allow for meaningful subpopulation analyses.

Endpoints to define outcome—The primary endpoint will be the development of one or more episodes of overt HE, which may or may not require hospitalisation. Other data pertinent to this primary endpoint, such as number of hospitalisations, LOS, HRQoL and cost analyses should also be collected. In addition, one or more of the objective markers detailed in the next section, such as psychometric testing or estimation of the critical flicker frequency (CFF) could be included, provided that the techniques can be standardised across centres

Trials in patients with minimal/covert HE

It was unanimously agreed that trials in patient with minimal/covert HE should be randomised and placebo-controlled, as in general these patients are not routinely treated.

Patient population—It was agreed that patients with a history of overt HE or treatment exposure should be excluded from these trials as treatment status has a significant confounding effect on the classification of neuropsychiatric performance.[34] Patients with overt HE may show few, if any, clinical abnormalities following treatment but retain some degree of neuropsychometric or neurophysiological impairment in the longer term.[3, 35, 36] These patients may be classified as having minimal HE but their responses to treatment will differ substantially from those diagnosed as having minimal HE *de novo*.[35]

Standard of care—These patients do not routinely receive treatment. Those who have a history of treatment exposure will be excluded from the study.

Endpoints to define outcome—The advantages and relative disadvantages of currently available tests for assessing neuropsychiatric performance in these patients were discussed in detail. In addition, their scientific merits, the logistics of their use and the associated cost were also considered.[32]

It was agreed that for single-centre or proof-of-concept studies, it is important that (i) the operators should be experienced in the use of the selected test(s); (ii) they should have experience in the administration of the tests and in the interpretation of the results; (iii) clear-cut, appropriate, normative reference data should be available; and (iv) the test should have been validated in the population under investigation. However, although use of appropriately validated but centre-specific test systems may be acceptable for use in these trials, the undertaking of multicentre studies requires use of sensitive, specific and validated methodologies that are widely available, easily accessible and affordable.

Neurophysiological techniques such as the EEG and somatosensory and cognitive evoked potentials provide objective data, which can be compared between centres.[11, 32] Patient co-operation is not required and the diagnostic performance of these tests continues to improve with the introduction of increasingly more sophisticated analytical techniques.[37] However, the equipment and the necessary operative/interpretive expertise needed to optimise use of these tests are not widely available, thereby limiting their use.

The PHES (Psychometric Hepatic Encephalopathy Score),[38] which consists of five paper–pencil tests, has been extensively validated and is used in several European countries. However, appropriate normative reference data are required and these are not available in the majority of countries, notably the US. In addition, differences in performance are observed in ethnic subgroups and there is currently no consensus on how the results of the Line Tracing Test should be processed.[39] Attention was also drawn to the fact that the performance of psychometric tests can be confounded by significant learning effects, even when multiple versions of the test are used.[40]

Assessment of the critical flicker frequency is relatively easily undertaken and has gained popularity. However, the results are influenced by a number of variables, such as age and gender requiring comparisons with normative population-specific reference data. Thresholds vary and have not been validated between centres. In addition, the results are equipment dependent with the sensitivity and specificity of results determined by differences in a number of variables including luminance and the colour of the transmitted light.[41, 42]

The computer-based inhibitory control test has been used in various forms in the US and in Europe with initial promise.[43, 44] However, even though the equipment has been standardised, there exists significant variation in the threshold levels identified for the measured variables and there is ongoing contention about how best to analyse the data.[45] The time taken to undertake the test and the intense concentration required also pose problems.

Thus, the majority of these surrogate markers present problems, although all have merit. Consensus on their standardisation and the interchangeability of their use are still required. In the interim, it is recommended that in multicentre trials in patients with minimal/covert HE, two or more of these tests are employed consistently across populations.

Recommendations for trials in patients with minimal/‘covert’ HE

- **i.** Trials in this population should be randomised and placebo controlled.
- **ii.** Patients receiving treatment for overt HE or those with prior episodes of overt HE should be excluded.
- **iii.** In single-centre or proof-of-concept studies, investigators may use tests for assessing the severity of HE with which they are familiar, provided that normative reference data are available and the tests have been validated for use in this patient population.

iv. Further information is needed on the interchangeability and standardisation of tests to assess the severity of HE for use in multicentre trials. As an interim, two or more of the current validated tests should be used and applied uniformly across centres.

Conclusion

Consensus was reached in this round table on a number of issues pertaining to the classification of the neuro-cognitive abnormalities, which may arise in patients with cirrhosis. It was generally agreed that such assessments, whether made clinically or more objectively, should be continuous rather than categorical, and a system for assessing the SONIC was proposed.[12] There was some dissent about the term to be used for patients with persistent but stable cognitive/motor abnormalities within this system but this will continue to be debated. Consensus was also reached on many aspects pertaining to the conduct of trials for assessing the treatment of HE, of varying severity, in patients with cirrhosis and for its secondary prevention. Patient populations, standards of care and trial endpoints were debated and agreed that some leeway will be required as there is significant intra- and inter-country variability in the availability of some of the more objective surrogate markers of HE, particularly psychometric testing and evaluation of the EEG. Areas for future debate were identified.

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Appendix

Non-trainees present during the 14th ISHEN roundtable:

Samir Ahboucha, Morocco

Arthur Cooper, USA

Vincente Felipo, Spain

Daniel Forton, UK

Robert Gribble, Australia

Rajiv Jalan, UK

Gerald Kircheis, Germany

Alan Lockwood, USA

Hanaan Mardini, UK

Sara Montagnese, Italy

Justin Nguyen, USA

Scott Nyberg, USA

Christopher Record, UK

Manuel Romero-Gomez, Spain

Christopher Rose, Canada

Sami Schiff, Italy

Misael Uribe, Mexico

Helen Vidot, Australia

Karin Weissenborn, Germany

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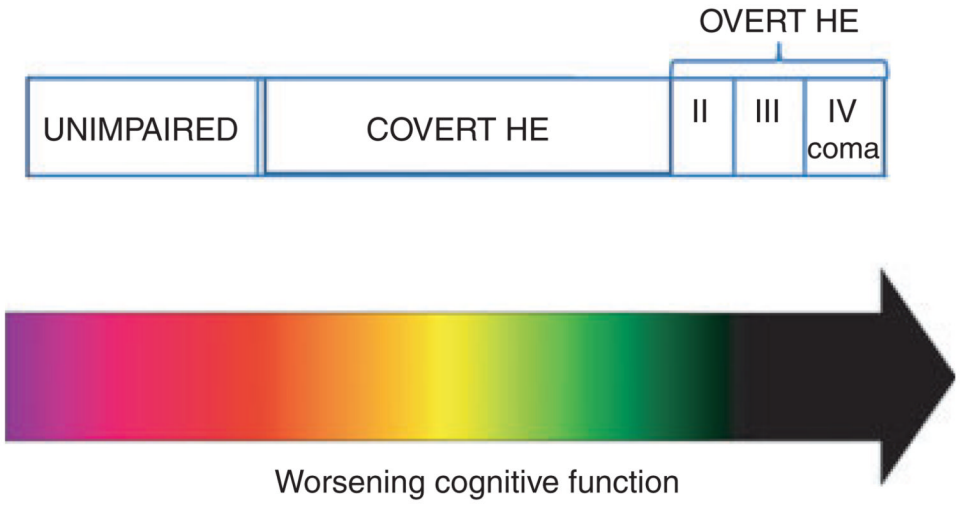

Figure 1.

Proposed classification of HE as part of inpatients with cirrhosis, by severity of the cognitive impairment. Patients with minimal HE and Grade I change using the West-Haven criteria[7] would be classified, as having COVERT HE. Patients with West-Haven Grade II changes or above would be classified as having OVERT HE. Patients with no clinical, neurophysiological or neuropsychometric changes would be classified as UNIMPAIRED.

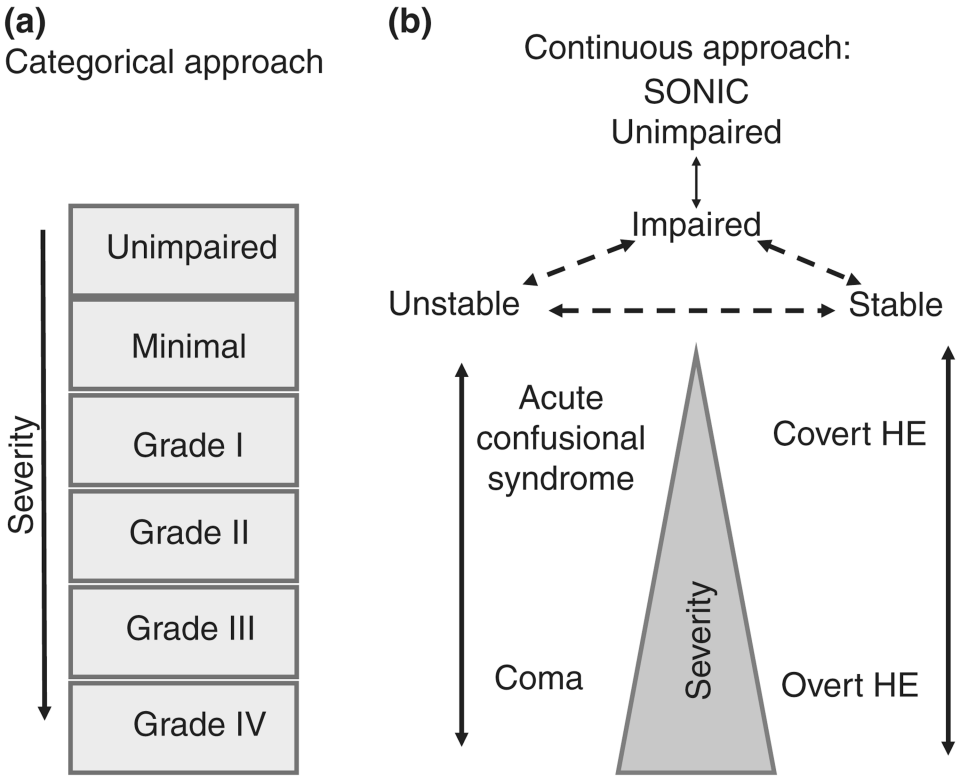

Figure 2.

Categorical and continuous approaches to the classification of hepatic encephalopathy in patients with cirrhosis. The assessment of cognitive function in HE can be performed using (a) categorical or (b) continuous approaches. (a) In the categorical approach, the criteria used to define the categories are arbitrary and have high inter-rater variability. (b) In the continuous approach, there are no fixed boundaries. Patients may be unimpaired or impaired; the impairment may be stable or unstable, and patients may move from one state to another over time. Those who are unstable would experience episodes of HE ranging from an acute confusional syndrome, by degrees to coma. Those that are impaired but stable may have no clinically discernable abnormalities but would exhibit neuro-psychometric/neurophysiological abnormalities on testing – covert HE or else would have obvious but stable clinical feature – overt HE. Individuals who have recovered from an episode of episodic HE may retain features of stable impairment, which may be either covert or overt. Those with prolonged and severe cognitive/motor deficits correspond to the patients who are currently classified as having persistent HE or acquired hepatocerebral degeneration. There is some overlap between the grades of the categorical approach and the situations defined in the continuous approach, but there is no direct correspondence. In the continuous approach, the assessment method is not limited by predefined reference categories.

Table 1

West Haven criteria for grading mental state in patients with cirrhosis*

Grade	Features
0	No abnormalities detected
I	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impairment of addition or subtraction
II	Lethargy or apathy
	Disorientation for time
	Obvious personality change
	Inappropriate behaviour
III	Somnolence to semi-stupor
	Responsive to stimuli
	Confused
	Gross disorientation
	Bizarre behaviour
IV	Coma, unable to test mental state

*The descriptions of the mental alterations in hepatic encephalopathy are those originally proposed by Conn *et al.*[7] as a modification of Parsons-Smith criteria.[8]

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Table 2
Proposed classification of the spectrum of neuro-cognitive impairment in cirrhosis

	Unimpaired	Covert HE	Overt HE
Mental status	Not impaired	Not impaired	From disorientation through coma
Specialised tests (according to local expertise)	Not impaired	Impaired	Not specifically required but will be abnormal
Asterixis	None	None	Present (except in coma)

The three major updated divisions of HE divided according to mental status, asterixis and specialised tests into unimpaired, covert HE and overt HE. Of note asterixis is absent in coma, which is the final stage of overt HE.